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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,158	12/05/2001	Wu-Bo Li	0942.4750003	3737

26111 7590 07/16/2002

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EXAMINER	
LOEB, BRONWEN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/002,158	Applicant(s) LI ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 05 December 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending.

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Drawings

2. The drawings are objected to because the word "oligonucleotide" is misspelled. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

3. Claims 2, 16 and 20 are objected to because of the following informalities: "Complementary" is misspelled in claim 2. In claim 16, the grammar would be improved by amending the claim to recite "said support in [~~of~~] said prestep (2)". Claim 20 recites an abbreviation which should be defined at its first use in the claim set. Appropriate correction is required.

4. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 recites the limitation "wherein said desired target nucleic acid molecule is a single-stranded nucleic acid". This limitation, however, is already recited in parent claim 1, line 3.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said desired target molecule" in lines 8 and 11. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 recites the limitation "said desired molecule" in line 18. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 recites the limitation "the template-dependent extension" in lines 12-13. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 recites the limitation "said probe molecules" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is vague and indefinite in reciting "a haptenylated nucleic acid probe molecule" followed by "said probe molecules". The first recitation is to a single probe molecule while the second, which presumably refers to the first recitation, is plural.

Claim 2 recites the limitation "said probe" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 recites the limitation "said...biotinylated probe-target hybridized molecules" in lines 15-16. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 recites the limitation "said haptenylated probe" in line 18. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 recites the limitation "said probe-target hybridized molecule" in line 21. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is vague and indefinite in reciting, in step (4), "releasing said hybridized target molecule". From the steps, it appears that what is released is single stranded target nucleic acid, not a hybridized target molecule, therefore this recitation renders the metes and bounds of the claim unclear.

Claim 3 recites the limitation "said single-stranded nucleic acid molecule" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites the limitation "said generated double-stranded molecules" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is vague and indefinite in reciting "incubating non-degraded nucleic acid". What is the nexus between this nucleic acid and the nucleic acid recited prior to this in claim 3?

Claim 3 is vague and indefinite in reciting "said primer" in line 12. Does this refer the primer recited in claim 3, lines 10-11 or to the primer recited in claim 1, lines 6-7?

Claim 4 recites the limitation "said sample" in line 22. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation "said initial sample" in line 25. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 is vague and indefinite in reciting "substantially unable to cleave", "substantially capable of degrading", "substantially eliminating" and "substantial enrichment of said desired target molecule". "Substantially" is a relative term which is not defined in the specification. Therefore the metes and bounds of the claim are unclear.

Claim 5 recites the limitation "said incubation" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites the limitation "said desired incubation" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1, 5, 7-12 and 25-27 are rejected under 35 U.S.C. §102(b) as being anticipated by Mullis et al (USP 4,800,159; IDS reference AA1). Mullis et al teach a method for recovering a desired target DNA wherein nucleic acid is incubated with a primer, double-stranded DNA (dsDNA) is generated by template-dependent extension of the primer (polymerase chain reaction; PCR) and the dsDNA is used to transform cells and the desired molecule is recovered. The nucleic acid may be DNA or RNA and may be either single stranded (ss) or double stranded (ds). The nucleic acid may be a circular nucleic acid molecule, such as a plasmid (a circular DNA molecule). See entire document, especially col. 6, line 12- col. 14, line 62.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

11. Claims 1, 2, 5-8, 10-19, 22, 23 and 25-27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Pruitt (Gene (1988) 66:121-134; IDS reference AT6) in view of Wieland et al (Proc. Natl. Acad. Sci. USA (1990) 87:2720-2724; IDS reference AR11) and Rubenstein et al (Nucleic Acids Research (1990) 18:4833-4842; ISD reference AT7).

Pruitt teaches a method of enriching clones whereby the clones are in the form of single stranded DNA, and are isolated by hybrid selection where the hybrid is recovered because the specific probe DNA is bound to a column. Pruitt transforms his recovered closed circular clones by transforming the ssDNA into a bacterial host, which differs from the double stranded DNA used in the instant invention. Rubenstein teaches the advantage of using dsDNA in transformation since it transforms with much higher efficiency and the making of dsDNA from ssDNA by primer mediated TAC polymerization, a well-known technique at the time the invention was made. It would have been obvious to one of ordinary skill at the time the invention was made to use the method of Rubenstein to convert the ssDNA of Pruitt to dsDNA, for the reason of increasing the efficiency of cloning, as in claim 1. It would have been a simple matter to use the method of Rubenstein, since sequence specific primers were made by Pruitt for their cloning procedure. Wieland teaches differential cloning where the target DNA is separated from the unwanted DNA by hybridization to a biotinylated probe, after which

this DNA is amplified by PCR, as in the instant invention, and cloned. The order of several of the procedures is not considered to be material to the invention unless otherwise shown to be so. For example, Wieland clones their recovered DNA onto a vector after recovery and amplification while in the instant invention the cloning (ligation) step is performed before initial recovery and amplification. One of ordinary skill would have known that changing the order of these steps would not have made a significant difference in the outcome of this procedure.

Conditions that minimize random hybridization are used in virtually all hybridization and cloning procedures, even hybridizations which are preformed at low stringency, and would have been self evident to one of ordinary skill for the purpose of increasing efficiency, as taught by many molecular biology manuals and texts. As in claim 8 and 11, the DNA molecule is circular ssDNA. Biotin/avidin is taught by Wieland for the purification of their clones, and streptavidin is only a particular well known form of avidin, used for the same purpose. Paramagnetic beads used for purification, e.g. when conjugated to biotin or avidin, are sold commercially, and had the known advantage of quick purification and simultaneous concentration. The position of primers on a target for the purposes of probing or as a primer for amplification was widely known to be easily changed and is considered immaterial unless shown to be otherwise. Such differences in position may have an effect on the efficiency of the process (e.g., amplification), but applicants have not shown that this would generally make any difference in their invention. PCR is used by Wieland and bacterial hosts in several reference teachings. Degenerate probes and primers are obvious modifications of the

invention widely used at the time to isolate sequences related to a known sequence, such as other members of a gene family or point mutations, etc.

12. Claims 3, 4, 21, 22 and 24 are rejected under 35 U.S.C. §103 as being unpatentable over Pruitt in view of Wieland et al (Wieland), and Rubenstein et al (Rubenstein) as applied to claims 1, 2, 5-8, 10-19, 23 and 25-27 above, and further in view of Vandeyar et al. (Gene (1988) 65:129-133; ISD reference AR10).

In addition to the other teachings of Rubenstein discussed above, Rubenstein also teaches elimination of background contaminating DNA by digesting with restriction enzymes that differentially recognize and digest the contaminating dsDNA because the ssDNA is not susceptible to the dsDNA specific enzymes used. This method is equivalent to using methyl sensitive restriction enzymes for this purpose, as in the instant invention. It was a widely known use of methyl sensitive restriction enzymes at the time the invention was made to differentially eliminate unwanted DNA, either in vivo or in vitro. Therefore, these enzymes were only being used for their known and recognized function. Motivation to use them as such comes from Rubenstein's teaching of elimination of background DNA, i.e. to increase the efficiency of the process. Vandeyar teaches removal of non-target nucleic acid in which the methylated (analog) strand of hemimethylated DNA is selectively removed by a nuclease before further cloning. The hemimethylated DNA is treated with a hemimethyl specific restriction enzyme to allow access for degradation by Exo III. Although more analogous to claim 3, it would have been an obvious and self evident modification to switch the DNA strand containing the methylated DNA or make the desired DNA fully methylated to prevent its

degradation. Furthermore, the methods of claims 3 and 4 and their dependent claims are expected to be functionally equivalent, since essentially the only difference is the level of methylation. It was well known that the enzyme *HhaI* cuts hemimethylated but not fully methylated DNA, so it would have been an obvious modification to make the invention of claim 4 rather than claim 3. The motivation to use this method is given by Vandeyar, that is to increase efficiency by reducing the amount of unwanted molecules.

13. Claim 9 is rejected under 35 U.S.C. §103 as being unpatentable over Pruitt in view of Wieland et al (Wieland), and Rubenstein et al (Rubenstein) as applied to claims 1, 2, 5-8, 10-19, 23 and 25-27 above, and further in view of Welcher et al. (Nucleic Acids Research (1986) 14:10027-10044; IDS reference AS11).

Welcher teaches hybridization of a probe to RNA, as in the instant claim. Motivation to combine the teachings of Welcher with the other reference teachings comes from the well known advantage of cloning with RNA as the starting material, since this allows for enrichment of coding regions of the genome compared to genomic cloning. Therefore it would have been obvious to one of ordinary skill at the time the invention was made to combine this teaching with the other reference teachings.

14. Claim 20 is rejected under 35 U.S.C. §103 as being unpatentable over Pruitt in view of Wieland et al (Wieland), and Rubenstein et al (Rubenstein) as applied to claims 1, 2, 5-8, 10-19, 21, and 25-27 above, and further in view of Rashtchian et al. (Analytical Biochemistry (1992) 206:91-97; IDS reference AR7).

Rashtchian teaches the elimination of undesired non-target nucleic acid sequences containing deoxyuridine by UDG. Motivation to adapt this method to that of

the instant invention is the self evident principal of eliminating undesirable molecules, thereby enriching for desired molecules which increases the efficiency of the process. This is the principal behind, for instance, selective PCR enrichment and cloning, as well as a host of other cloning techniques. Therefore, it would have been obvious to one of ordinary skill at the time the invention was made to combine the instant reference teaching with those made of record above.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 2, 6, 13-19 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8-13 and 17 of U.S. Patent No. 5,500,356. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant application recite steps also recited in the allowed claims of USP 5, 500,356, which recite additional

steps. Essentially the pending claims are generic to the allowed claims and are therefore rendered obvious by them.

17. Claims 1, 2, 6, 7 and 13-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 20, 23-28, 40 and 41 of U.S. Patent No. 5,759,778. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant application recite steps also recited in the allowed claims of USP 5, 759,778, which recite additional steps. Essentially the pending claims are generic to the allowed claims and are therefore rendered obvious by them.

18. Claims 2 and 6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 28 and 43 of copending Application No. 09/018,989. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant application recite steps also recited in the pending claims in Application No. 09/018,989, which recite additional steps. Essentially the pending claims are generic to the allowed claims and are therefore rendered obvious by them.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-27 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

July 15, 2002

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